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Reboxetine: A Selective Norepinephrine Reuptake Inhibitor for the Treatment of Depression

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OBJECTIVE: To review the pharmacology, pharmacokinetics, efficacy, and tolerability of reboxetine in the treatment of major depressive illness.

DATA SOURCES: A MEDLINE search restricted to English-language literature was conducted (1966 to July 1999). Abstracts and posters presented at meetings were also reviewed.

DATA EXTRACTION/STUDY SELECTION: Studies currently available were conducted in Europe. Data from clinical trials were reviewed to gather information specific to efficacy analysis, pharmacokinetic parameters, tolerability profiles, and drug–drug interactions. Information on reboxetine was compared with other antidepressant therapies when appropriate data were available.

DATA SYNTHESIS: Reboxetine is a selective norepinephrine reuptake inhibitor shown to be an effective agent in the treatment of major depressive illness. In clinical trials, reboxetine was effective in decreasing mean total scores of the Hamilton Rating Scale for Depression in adult populations. Improvements were similar between reboxetine and desipramine and imipramine, as well as fluoxetine. Reboxetine is relatively well tolerated, with insomnia, sweating, constipation, and dry mouth being commonly reported adverse events. Hypotension and urinary hesitancy occur at lower rates than with the tricyclics, and compared with fluoxetine, reboxetine is associated with lower rates of nausea, somnolence, and diarrhea. Dosage adjustments may be appropriate in elderly patients and those with renal and hepatic impairment.

CONCLUSIONS: Reboxetine has received two letters of approval from the Food and Drug Administration for the treatment of major depression in adults. Upon completion of an additional US clinical study, reboxetine is likely to become a first-line agent in the management of depressive illness and a promising alternative for patients who have failed treatment with or do not tolerate serotonergic antidepressants.

KEY WORDS: reboxetine, depression.

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The current therapeutic goal in the treatment of major depression is to improve the quality of life by normalizing mood, increasing awareness of personal pleasures and interests, and reversing the functional and social disabilities associated with depression, as well as to reduce suicide rates. The lifetime prevalence of major depression in the US has been estimated to be approximately 17%, with an estimated 20–25 million individuals suffering from depressive disorders. Women and patients with chronic medical illnesses or loss of independence are at higher risk for developing depression.[1] There are approximately 30 000 suicides annually in the US, with one attempt every 15 minutes. According to data analyzed from 1990,[2] the total annual costs associated with caring for patients with depression were estimated at more than $40 billion. Schematically, mood disorders may be classified into distinct entities such as major depression, dysthymia, "double" or chronic depressions (major depression superimposed on dysthymia), bipolar disorder, premenstrual dysphoric disorder, minor depression, atypical depression, mood disorders with seasonal variation, and mood disorders due to a general medical condition (previously known as organic mood disorder). Major depression is a chronic illness and, when left untreated, episodes can last from months to several years. Relapses and recurrences may follow initial episodes. Currently, most patients with major depression are treated in primary care and, for various reasons, depression remains underdiagnosed and undertreated.

Major depression appears to be a syndrome with genetic, biochemical, and clinical heterogeneity. Although we do not yet fully know the brain mechanisms that lead to the development of depression and its symptoms, exten-

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Reboxetine (Vestra, Pharmacia & Upjohn).

sive research supports various theories on the neurochemistry of depression. The catecholamine theory proposes that there is an absolute or relative deficiency of catecholamines, such as norepinephrine, at functionally important receptor sites in the brain.[3] The locus ceruleus is a key source of noradrenergic innervation to the frontal and motivational circuits of the human brain and is dysregulated in depression. The indoleamine theory suggests that there is a deficiency in the amount of serotonin available to the central nervous system (CNS).[4] Another hypothesis proposes that alterations in neuropeptide regulation in the brain mediate depression. A prominent theory suggests that there is a relative increase in corticotropin-releasing factor, causing an overdrive of the hypothalamic–pituitary–adrenal axis and hippocampal damage.[5] Regardless of these theories, it is possible that many of these systems are interlinked in the brain and may have overlapping clinical or behavioral effects. Therefore, subgroups of major depressive patients may respond differently to noradrenergic, serotonergic, or dopaminergic agents. Also, there may be subgroups of patients who respond best to agents with effects on several combinations of these systems. Thus, several different classes of newer antidepressants have been developed with varying effects on neurotransmitters (Table 1).

Targeting the noradrenergic system as a treatment mechanism for depression has evolved both from serendipitous observations as well as from preclinical and clinical pharmacologic research studies. Tricyclic antidepressants (TCAs) such as desipramine are relatively selective for inhibiting the reuptake of presynaptic norepinephrine, with a minor role in the potentiation of serotonin. In addition, these medications have affinity for muscarinic, α-adrenergic, and histaminergic receptors.[6] The involvement of these additional neuronal receptors leads to the development of common adverse effects associated with TCA administration including dry mouth, constipation, cardiac arrhythmia, orthostatic hypotension, and sedation. Irreversible monoamine oxidase inhibitors (MAOIs) also enhance central noradrenergic function by inhibiting norepinephrine metabolism. However, these agents have fallen out of favor as first-line treatment options secondary to potentially harmful adverse effects (e.g., hypertensive crisis) and stringent dietary restrictions (e.g., avoid tyramine-containing foods).[7] With the desire to have improved safety and tolerability profiles among the agents used to treat depression, selective serotonin-reuptake inhibitors (SSRIs) were developed. These medications are highly selective for inhibiting the reuptake of serotonin; therefore, patients typically do not experience many of the central and autonomic adverse effects associated with older antidepressants. The adverse effects commonly noted with SSRI therapy include various gastrointestinal manifestations, sleep disturbances, and sexual dysfunction.[7,8] In addition, antidepressants have the pharmacokinetic potential to interact with medications that rely on the cytochrome P450 systems for metabolism via the liver. One of the latest investigational agents, reboxetine mesylate, received a letter of approval from the Food and Drug Administration (FDA) in July 1999. Reboxetine is currently available in European countries to treat depression. Reboxetine is a potent and selective norepinephrine reuptake inhibitor (NRI) with minimal or no effects, in vitro, on the serotonergic or muscarinic systems.[9] Table 2 illustrates selective norepinephrine and serotonin reuptake for reboxetine in comparison with other common antidepressants.[9-12]

Chemistry

Reboxetine mesylate is a racemic mixture and both enantiomers are active (Figure 1). Data show the *S,S* (+) enantiomer to be more potent at norepinephrine reuptake inhibition, although the *R,R* (–) enantiomer is present in plasma concentrations twofold those of the *S,S* (+) enantiomer.[13,14] No chiral inversion occurs in vivo, and there does not appear to be an interaction between the two enantio-

Table 1. Antidepressant Medication Classes

Tricyclic antidepressants (nonselective NE and/or 5-HT reuptake inhibitor)	Selective serotonin-reuptake inhibitors
amitriptyline	citalopram
amoxapine	fluoxetine
clomipramine	fluvoxamine
desipramine	paroxetine
doxepin	sertraline
imipramine	Aminoketone (NE and DA uptake inhibitor)
nortriptyline	bupropion
protriptyline	Phenethylamine (5-HT, NE, and DA uptake inhibitor)
trimipramine	venlafaxine
Tetracyclic antidepressants	Other (5-HT reuptake inhibitor and antagonist)
maprotiline (presynaptic NE reuptake inhibitor)	nefazodone
Monoamine oxidase inhibitors	trazodone
phenelzine	mirtazapine (plus α_2-antagonist)
tranylcypromine	Selective norepinephrine reuptake inhibitor
	reboxetine

DA = dopamine; 5-HT = serotonin; NE = norepinephrine.

Table 2. Comparative Neurotransmitter Reuptake Selectivity of Select Antidepressants[9-12,a]

Drug	Potency for Inhibition of NE Reuptake (nmol)	Potency for Inhibition of 5-HT Reuptake (nmol)	Ratio of Potencies for Inhibiting NE Relative to 5-HT
Reboxetine	8	1070	0.007
Desipramine	14	1200	0.012
Venlafaxine	213	39	5.5
Fluoxetine	500	25	20.0
Sertraline	1400	7	200.0

5-HT = serotonin; NE = norepinephrine.
[a]Smaller numbers indicate higher potency since a lower concentration (in nmol) is required to achieve the tested effect.

mers.[13] Reboxetine is chemically unrelated to tricyclic or tetracyclic antidepressants, MAOIs, or SSRIs.

Pharmacology

As discussed previously, data indicate that patients with depression have defective regulation of noradrenergic neurons within the CNS, particularly the cerebral cortex and thalamic–hypothalamic regions, as well as the limbic system. Therefore, targeting norepinephrine appears to be an appropriate mechanism for treating depressive illness. The noradrenergic system appears to be primarily involved in regulating the sleep–arousal cycle, consciousness, learning and memory, appetite, sex, anxiety, and sensory perception. Therefore, imbalances in the noradrenergic system can lead to symptoms characteristic of depression.[15] Reboxetine is a selective NRI that is also a weak inhibitor of serotonin, lacks dopamine activity, and has no significant affinity for adrenergic, histaminergic, or cholinergic receptors.[9] The lack of these receptor affinities may explain the low appearance of anticholinergic, cardiovascular, and sedative adverse effects linked to reboxetine therapy. By inhibiting norepinephrine reuptake, reboxetine causes an acute increase of synaptic concentrations of norepinephrine followed by a down-regulation and desensitization of β- and α_2-receptors, coupled with an increase in responsiveness of postsynaptic α_1-receptors. It is via this modification of the noradrenergic system that reboxetine is believed to exert its antidepressant activity.[10] It is not necessary to monitor plasma concentrations of reboxetine because there are no defined plasma concentrations that correlate with therapeutic effect.

Pharmacokinetics

Pharmacokinetic data comparing reboxetine with other antidepressants are summarized in Table 3.[13,16-19]

ABSORPTION

Within the therapeutic range studied (1–8 mg/d), reboxetine follows linear kinetics; therefore, changes in drug plasma concentration increase linearly with increases in dosage.[13,20,21] Reboxetine is rapidly absorbed following oral administration, with an oral bioavailability >92%.[14] Mean peak plasma concentrations of 111 ng/mL have been documented to occur approximately two hours after a dose.[14,20,21] Reboxetine appears to be highly protein bound, with 96% binding to α_1 acid glycoprotein.[21]

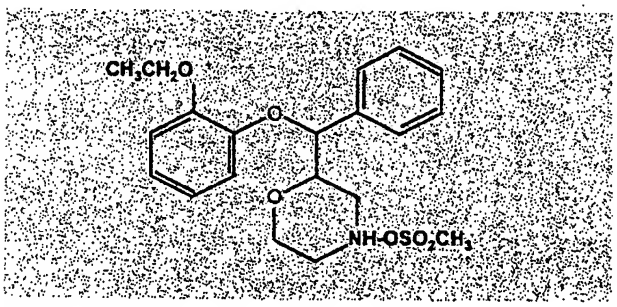

Figure 1. Graphic formula of reboxetine mesylate.

FOOD

Following a high-fat meal, the mean peak plasma concentration of reboxetine was slightly reduced (from 125 to 104 ng/mL); however, the overall bioavailability was not affected.[20] Therefore, food does not appear to significantly affect the extent of reboxetine absorption.

METABOLISM

Reboxetine is extensively metabolized via the liver through three major routes: hydroxylation of the ethoxyphenoxy ring, oxidative dealkylation, and oxidation of the morpholine ring.[22] In vitro studies[23] indicate that reboxetine is metabolized by the cytochrome P450 isoenzyme system, particularly the subfamily CYP3A4. CYP2D6 does not appear to be involved in the metabolism of reboxetine. This is based on the results of a study[13] that evaluated plasma kinetics of reboxetine following concurrent administration of reboxetine and quinidine (a known potent inhibitor of CYP2D6). The researchers did not find significant changes in reboxetine pharmacokinetics. In vitro studies[13,24] have shown that reboxetine does not inhibit the following isoenzymes of cytochrome P450: 1A2, 2C9, 2C19, or 2E1 at dosages well above the therapeutic range. Weak inhibition of CYP2D6 and CYP3A4 is possible; however, based on available data and postmarketing experience in Europe, the potential for a serious in vivo interaction is unlikely.[23]

ELIMINATION

The elimination half-life ($t_{1/2}$) of reboxetine is approximately 12–13 hours following both single and multiple doses.[20,21] Data obtained from both animal and human studies[22] illustrate that the dominant pathway for excretion of metabolites and unchanged drug appear to be renal mechanisms, with lesser amounts eliminated via the feces. Approximately 9% of orally administered reboxetine is excreted unchanged in the urine[20]; the renal clearance is estimated to be 3 mL/min.[20,21]

Special Populations

HEPATIC/RENAL IMPAIRMENT

Data suggest that patients with liver impairment may require dosage adjustments. A small population of patients with moderate (n = 6) and severe (n = 6) hepatic impairment (grades B and C Child–Pugh classification, respectively) participated in a study[13] to assess the potential impact of liver disease on reboxetine dosing. The AUC and $t_{1/2}$ were determined to be higher when compared with values obained from healthy volunteers. Patients with grade B impairment experienced a 24% higher increase in AUC;

grade C patients had increases 36% greater than the healthy group. The $t_{1/2}$ values were reported as 21, 31, and 17 hours, respectively. Therefore, the metabolic clearance of reboxetine may be affected in patients with hepatic impairment.

Patients with renal impairment may need to use lower daily dosages of reboxetine. It appears that the renal clearance of reboxetine decreases while the bioavailability increases in patients with moderate (creatinine clearance 56–80 mL/min), medium (creatinine clearance 26–50 mL/min), and severe (creatinine clearance 9–20 mL/min) renal impairment.[13,25]

ELDERLY

One study[13] assessed the pharmacokinetics of reboxetine in 12 depressed, elderly patients. Subjects were administered reboxetine 1 mg twice daily for one week, with subsequent weekly dosage increases of 1 mg twice daily until a dosage level of 4 mg given twice daily was achieved. The authors noted a large interpatient variability among the parameters assessed (mean peak plasma concentration, minimum concentration, average concentration, AUC_{0-12h}; therefore, as a precaution it is recommended that elderly subjects receive lower initial daily dosages of reboxetine.

Pharmacokinetic data were pooled from studies enrolling patients and healthy volunteers from five age groups (21–39, 50–63, 68–77, 66–98, 75–87 y) who were administered reboxetine 4–8 mg/d.[26] These data also revealed variable differences in reported AUC and $t_{1/2}$ compared with the sample of 15 young, healthy men (21–39 y). There appeared to be slight increases in kinetic parameters with increasing age, but overall, reboxetine was well tolerated. An initial dosage of 2 mg twice daily appears to be appropriate for use in elderly patients.

Gender

In a small study[14] with six male and six female healthy volunteers, reboxetine administration did not result in clinically significant differences between genders in pharmacokinetic parameters. The peak plasma concentration following oral administration was 40–48% higher in women than men for both enantiomers ($p < 0.05$). Parameters that were not found to be statistically different included measures of bioavailability, time to peak concentrations, and $t_{1/2}$.

Clinical Trials

Treatment of depression is categorized into acute, continuation, and maintenance phases. Current guidelines for the treatment of depression recommend an acute phase of treatment at optimal dosages (usually 6–12 wk) until remission. This phase should be followed by a continuation phase (usually 6–12 mo) in which therapy is continued at the same dosage used to achieve remission in order to prevent relapse. In addition, some patients may need maintenance treatment (several years) to prevent recurrent episodes.[27,28] Long-term therapy should be considered for patients with risk factors such as a history of two or more episodes of depression, a family history of depression, past suicide attempts, comorbid substance abuse, and/or personality disorders. Thus, it is important to evaluate data reported in the literature on the effect of a given antidepressant in each of these phases.

Inpatients and outpatients with a diagnosis of major depressive disorder according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-III[29] or DSM-III-R[30] criteria participated in clinical trials[31-34] comparing the efficacy and tolerability of reboxetine with placebo and/or comparator agents. In these trials, reboxetine demonstrated similar efficacy to other antidepressants (Table 4)[31-34] and superior efficacy compared with placebo.[35] The primary measure of clinical efficacy was the Hamilton Rating Scale for Depression (HAM-D). Reductions in the HAM-D total score as well as the percentage of responders (≥50% reductions in HAM-D total score) to reboxetine therapy were measured to assess the ability of reboxetine to treat depressive disorder. Other scales used to assess patient response to therapy were the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impression (CGI) scale. The MADRS is frequently used in European regulatory trials as a primary outcome measure. The CGI

Table 3. Pharmacokinetic Parameters of Reboxetine in Comparison with Other Antidepressants[13,16-19]

Parameter	Reboxetine	Amitriptyline	Desipramine	Fluoxetine	Sertraline	Venlafaxine
Bioavailability (%)	94	40–60	50	95	90	45
C_{max} (ng/mL)	111	50–150	75–150	15–55	123–165	150[a]
Protein binding (%)	96	96	90	95	98	30
$t_{1/2}$ (h)						
parent compound	13	9–25	14–25	24–72	26	5
metabolite	NA	15–39	22	4–16 d	62–104	11
t_{max} (h)	2	2–4	4–6	6–8	5–8	6–9[a]
Time to reach steady-state (d)	3–5	7	7	28	7	3
V_d (L/kg)	34	16	15–37	3–40	20	6–8
% Unchanged in urine	9	5	<20	5–10	none	<10

C_{max} = peak plasma concentration; NA = not applicable; $t_{1/2}$ = half-life; t_{max} = time to maximum concentration; V_d = volume of distribution.
[a]Extended-release preparation.

comprises separate ratings of depression severity (CGI-S) and improvement (CGI-I).

ACUTE TREATMENT OF DEPRESSION

Reboxetine versus Desipramine versus Placebo

Ban et al.[31] showed that reboxetine 4–8 mg/d was an effective option for treating hospitalized patients with major depression in a double-blind, placebo-controlled, multicenter study. Patients (n = 258) with major depression (DSM-III-R) who had scores of at least 16 on the 17-item HAM-D were enrolled to assess the efficacy and tolerability of reboxetine compared with desipramine, which is also primarily a noradrenergic agent. Patients completed a seven- to 14-day washout phase prior to initiating therapy with daily dosages of reboxetine 4–8 mg (n = 84), desipramine 100–200 mg (n = 89), or placebo (n = 85) for four weeks. Therapeutic responses were primarily determined by score reductions of at least 50% on the HAM-D scale.

Sixty percent of the patients receiving reboxetine demonstrated a therapeutic response compared with 35% of those taking placebo ($p < 0.05$). In comparison, 48% of the patients taking desipramine showed a ≥50% decrease in HAM-D scores. Patients taking both reboxetine and desipramine had significantly higher response rates ($p < 0.05$) than placebo when assessed using MADRS (66.2%, 54.9% vs. 35.8%, respectively) and CGI-S (51.2%, 35.0%, vs. 22.5%, respectively). The onset of therapeutic effect was determined to be from days 10 to 14 with reboxetine; desipramine demonstrated a relatively later onset of effect at days 14–28, depending on the rating scale used. The lower response rates noted with desipramine therapy could have resulted from the short duration (4 wk) of this trial. Of the 258 patients initially enrolled, 233 completed the clinical trial; 18 patients stopped therapy because of ineffective treatment and four patients refused treatment. Adverse effects resulted in the withdrawal of two reboxetine-treated patients (ventricular systoles/constipation, hypertension/blurred vision/constipation/drowsiness) and one placebo-treated patient (skin rash).[31]

With regard to tolerability, events with moderate to marked severity noted to occur in at least 5% of the population administered desipramine included constipation, insomnia, and hypotension; reboxetine-treated patients reported constipation, insomnia, and tachycardia. Dry mouth and blurred vision were documented more often by subjects receiving desipramine than those on reboxetine or placebo. Urinary hesitancy was noted more often in patients taking reboxetine than those taking placebo, but not significantly more than with desipramine. Adverse effects of moderate severity (e.g., dry mouth, constipation) occurred more frequently ($p < 0.05$) in patients who received desipramine or reboxetine than in those who received placebo.[31]

This study is noteworthy because it is one of few published trials of a newer antidepressant in hospitalized depressed patients. The fairly robust response rate (60%), despite a short treatment period (4 wk), suggests that reboxetine may be a treatment of choice in psychiatric inpatient settings, which receive considerable pressure from managed care organizations to limit hospital stays.[31]

Table 4. Summary of Comparative Clinical Trials

Reference	Drug	Dose (mg/d)	Number of Patients	Duration of Trial (wk)	Mean Change in HAM-D Score	p Value	Percent Responders	p Value
					baseline / day 14[a]			
Ban et al. (1998)[31] hospitalized patients	reboxetine	4–8	84	4	28.8 / 16.35	<0.05[b]	60	<0.05[c]
	desipramine	100–200	89		NR		48	
	placebo		85		25.43 / 19.54		35	
					baseline / day 42			
Berzewski et al. (1997)[32] hospitalized and outpatients	reboxetine	4–10	130	6	28.8 / 9.6	NR	68.5	[d]
	imipramine	150–200	126		28.0 / 10.4		56.2	
					absolute change			
Massana (1998)[33] outpatients	reboxetine	4–10	126	8	13.4	<0.024[e]	56	<0.01[e]
	fluoxetine	20–40	127		13.3		56	
	placebo		128		8.6		34	
					baseline / last			
Massana et al. (1999)[34] hospitalized and outpatients	reboxetine	4–10	79	8	28.6 / 9.4	NS	78	NR
	fluoxetine	20–40	89		27.4 / 10.6		74	

HAM-D = Hamilton Rating Scale for Depression; NR = not reported; NS = not significant, 95% CI −0.3 to 5.1.
[a]No HAM-D scores provided at 4 weeks.
[b]Significant difference identified between reboxetine and placebo.
[c]Significant difference identified between reboxetine and placebo; not significant between reboxetine and desipramine.
[d]Significant difference compared with imipramine (95% CI 0.3 to 24.3); no p value provided.
[e]Significant difference identified for reboxetine vs. placebo and fluoxetine vs. placebo.

REBOXETINE VERSUS IMIPRAMINE

Berzewski et al.[32] conducted a six-week, double-blind, randomized, multicenter trial to compare the efficacy and tolerability of reboxetine with that of imipramine in adults (18–65 y old) with major depression (DSM-III-R, 21-item HAM-D ≥22). Treatment consisted of reboxetine 4–10 mg (n = 130) or imipramine 150–200 mg (n = 126) in divided daily doses for six weeks. If there was an unsatisfactory response with reboxetine 8 mg or imipramine 150 mg after three weeks of therapy, but patients appeared to tolerate the medication, the daily doses were increased to 10 mg of reboxetine (n = 13) or 200 mg of imipramine (n = 16). The desired primary efficacy measure was a decrease in total HAM-D score.

After six weeks of treatment, mean HAM-D scores improved from 28.8 and 28.0 to 9.6 and 10.4 for subjects treated with reboxetine and imipramine, respectively. Sixty-nine percent of patients treated with reboxetine and 56% of patients treated with imipramine were considered responders (≥50% decrease in HAM-D). Fifty-two percent of the reboxetine patients and 45.5% of the imipramine patients were defined as in remission, based on achieving a HAM-D score ≤10. MADRS scores declined from 17.2 and 16.9 to 5.9 and 6.0 for reboxetine- and imipramine-treated patients, respectively. Response among a subset of patients rated on the CGI-S to have severe depression (80% of reboxetine, 72% of imipramine patients) was similar to that of the entire population.[32]

The most commonly reported adverse effects in these patients included dry mouth (25% reboxetine vs. 36% imipramine), headache (16% vs. 14%), nausea (15% vs. 11%), increased sweating (14% both), constipation (10% both), and hypotension (10% vs. 18%). Adverse events occurring with significantly higher frequency following imipramine therapy included dry mouth, hypotension, and tremor ($p < 0.05$). Thirteen reboxetine- and 18 imipramine-treated patients withdrew from the trial secondary to adverse events. The most common reasons given for discontinuing reboxetine therapy included insomnia, dizziness, headache, nausea, sweating, and/or urinary retention. Adverse effects associated with discontinuing imipramine therapy included tachycardia, headache, dry mouth, tremor, fatigue, dizziness, asthenia, confusion, somnolence, sweating, and/or urinary retention.[32]

This study confirms that reboxetine is at least as effective as the relatively nonselective agent imipramine at treating major depression. The inclusion of both hospitalized and nonhospitalized patients is a strength of this trial and allows greater generalizability. Data on the "severe" subgroup as well as on rates of "remission" should be interpreted in the context of the definitions used in this study.

REBOXETINE VERSUS FLUOXETINE WITH AND WITHOUT PLACEBO

Massana et al.[33,34] reported data from two multicenter, double-blind studies that were conducted to determine the efficacy of reboxetine compared with that of fluoxetine in patients (n = 549) under inpatient or outpatient care with scores of at least 22 on the 21-item HAM-D scale. Patients completed washout phases of up to four weeks before receiving therapy for eight weeks with reboxetine (8–10 mg/d) or fluoxetine (20–40 mg/d), with one study[33] having a placebo comparative group. The primary efficacy measure was a decrease in HAM-D total score after the completion of treatment. Patients who had reductions in HAM-D total scores by at least 50% from baseline were considered to be responders to treatment.

Cumulative analysis of these two studies showed that the incidence of adverse events was similar among patients administered reboxetine (67%), fluoxetine (66%), and placebo (61%). Nausea and vomiting were reported most frequently by patients taking fluoxetine (25%) compared with patients taking reboxetine (15%) or placebo (13%). Constipation, sweating, and hypotension were reported most often by those administered reboxetine (17%, 12%, and 13%, respectively); <10% of the comparator subjects reported these events. Insomnia (16%) and dry mouth (27%) were documented more frequently with reboxetine therapy in comparison with fluoxetine (11% and 6%) and placebo (6% and 14%). Fluoxetine-treated subjects reported headache more than either reboxetine- or placebo-treated subjects (20%, 14%, and 15%, respectively).[33,34]

Reboxetine and fluoxetine demonstrated comparable efficacy with similar reductions in mean HAM-D total scores; both active treatment groups produced significantly better responses than placebo ($p < 0.024$). Score reductions of 13.4 were documented for patients administered reboxetine compared with 13.3 for the fluoxetine-treated patients; subjects who received placebo had reductions of 8.6.[33,34] In the placebo-controlled study,[33] significantly more patients administered reboxetine or fluoxetine (56%) were considered responders to treatment compared with 34% of patients given placebo ($p < 0.01$). In the study with nonplacebo control group,[34] 78% of reboxetine-treated patients and 74% of fluoxetine-treated patients responded to treatment.

Social Adaptation and Functioning

Depression can profoundly impair functional behavior and social interactions. Therefore, measures to assess the ability of antidepressants to restore daily functional capacity and quality of life in both the home and work settings may be important tools. One of the secondary outcome measures used in the two studies[33,34] that compared reboxetine with fluoxetine was the Social Adaptation Self-Evaluation Scale (SASS).[33] This 21-item self-rated questionnaire, developed in Europe, includes questions on work interests, involvement in hobbies, family and friend relationships, as well as self and environmental perceptions.[36] In both studies, active treatment was associated with improvements in SASS scores at end point, suggesting that the SASS measures domains that improve in relation to improvements in depression. In the study with a placebo control group,[33] reboxetine produced larger SASS improvements than fluoxetine or placebo. In the trial without placebo control,[34] SASS scores im-

proved in both the reboxetine (31% improvement) and fluoxetine (26% improvement) groups, but there were no statistically significant differences between the two drugs. The SASS has not been fully evaluated in US outcome studies; hence, its clinical significance is uncertain at present.

Several conclusions can be drawn from these two studies: reboxetine has similar efficacy and overall rates of adverse effects compared with fluoxetine, supporting the value of both as first-line agents; the parallel efficacy of an NRI and SSRI suggest that there may be a different final common pathway, as yet unidentified, that mediates the effects of both agents; there are some specific differences in adverse effect profiles of reboxetine and fluoxetine that may be used to choose an appropriate therapeutic option (e.g., when switching drugs for patients who are intolerant). The data on SASS should be considered preliminary but promising in light of the need to develop broader measures of the effectiveness of antidepressant therapy, rather than only depression ratings, and the theoretical links between norepinephrine, motivation, and social functioning.

Relapse and Recurrence

LONG-TERM EFFICACY STUDY

Studies have shown that major depressive illness is a chronic condition, which requires ongoing treatment and, in some patients, maintenance therapy to guard against relapse and recurrence of illness. It has been estimated that once a patient has experienced one episode of depressive illness, there is >50% chance that a second episode will occur. Subsequently, there may be an 80–90% probability of a third episode occurring.[28] Patients should continue pharmacologic treatment after an acute response for an extended period of time (at least 6–12 mo) to reduce the risk of relapse. Studies[37] suggest that relapses are most likely to occur during the first eight weeks after discontinuation of medication. However, the exact length of time that treatment is necessary to prevent recurrence of depression remains controversial and should be based on clinical judgment. As stated previously, maintenance therapy must be considered for patients with a family history of depression, two or more prior episodes of depression, past suicidal tendencies, and those with comorbid disorders. Should a patient become refractory to therapy, the clinician may choose to switch to another antidepressant or augment the first agent by adding a second one, depending on cost and adverse-effect issues.

Versiani et al.[38] conducted a randomized, double-blind, placebo-controlled study to examine the long-term efficacy and tolerability of reboxetine therapy in patients with a diagnosis of acute recurrence of major depressive disorder (DSM-III-R). In an initial open-label phase of the trial, patients had responded (≥50% decrease from baseline on 21-item HAM-D) to six weeks of treatment with reboxetine 8 mg/d. The mean ± SD HAM-D total score decreased from a baseline of 29.6 ± 5.6 to 11.4 (no SD indicated) by week 6. Patients also reflected improvement by improving scores on the MADRS, Zung, and CGI assessments. After this initial treatment phase, patients (18–65 y old) were randomized to continue therapy with reboxetine 4 mg administered twice daily (n = 143) or receive placebo (n = 140) for an additional 46 weeks to determine time to relapse and relapse rates. The data were also divided into the first and second six months of therapy to examine relapse rates. In addition, HAM-D, CGI, MADRS, and Zung scores were monitored.

One hundred forty-four patients completed the study, with 64 reboxetine patients and 75 placebo patients discontinuing therapy. Reasons for halting therapy included the occurrence of adverse events (6 reboxetine, 2 placebo) and lack of efficacy (17 reboxetine, 36 placebo). Following the 46-week long-term phase of the trial, remission of depressive symptoms was evident in 78% of patients taking reboxetine and 44% of those on placebo ($p < 0.001$). Relapse, characterized by a rapid worsening of depressive symptoms, was noted in 56% of patients receiving placebo and 22% of those treated with reboxetine ($p < 0.001$).[38]

During the first six months as well as the second six months of treatment, reboxetine was successful in preventing relapse in significantly more patients when compared with placebo. Sixty-one percent of patients administered reboxetine during the initial six months remained relapse-free; 40% of those on placebo were successful ($p \leq 0.001$). Of those patients maintained on therapy during the final six months of the trial, 88% of reboxetine patients and 59% of placebo patients remained relapse-free ($p \leq 0.001$). The greatest risk of relapsing appeared to occur during the first three to four months without therapy.[38]

Baseline mean total HAM-D scores for patients randomized to long-term therapy with reboxetine were 8.8 at the completion of the initial open-label phase. These scores declined to a mean of 7.9 at the final 46-week assessment. This is in comparison with patients randomized to receive placebo; baseline mean HAM-D score was 9.1 at the end of the six-week open-label phase in this group, which increased to 13.9 at the final 46 weeks' assessment, indicating that depressive symptomatology progressed without continued treatment. Active drug therapy also impacted MADRS and Zung assessment scores. At week 6, mean baseline MADRS scores were 5.25, which further improved to a mean of 4.47 at the end of the 46-week phase of the trial, while placebo-treated patients had increases from a mean of 5.25 to 8.58. Zung scores improved with reboxetine therapy, while placebo resulted in a worsening of depressive illness at the final assessment. Therefore, the majority of patients who remained on reboxetine therapy for the duration of the long-term phase of the study did not relapse compared with those randomized to receive placebo.[38]

During the initial open-label phase, the commonly observed adverse effects included dry mouth (19%), constipation (16.3%), increased sweating (8.1%), tachycardia (6.1%), insomnia (6.1%), urinary retention/hesitation (5.6%), and decreased libido (5%). Events that led patients to stop therapy included tachycardia (4 pts.), dry mouth, constipation, decreased libido, and urinary retention/hesitancy (2 pts. each). During the long-term phase of the trial, adverse

events that resulted in patients discontinuing reboxetine therapy were dry mouth (2 pts.), constipation (3), decreased libido (2), and urinary retention/hesitancy (1). One patient administered placebo discontinued the trial secondary to constipation. Ten percent to 15% of patients on reboxetine experienced increased heart rate, but this was not judged to be clinically significant. Two serious adversities occurred in patients taking reboxetine therapy: one patient committed suicide by multiple drug overdose and one experienced a generalized convulsive episode.[38]

Reboxetine has demonstrated efficacy in the maintenance therapy (52 wk) of elderly patients (aged 65–94 y) with major depressive disorder or dysthymia. The mean HAM-D total score showed a reduction from 24.0 at baseline to 7.5 at week 52. The most frequently documented adverse effects were nausea (11.9%), insomnia (11.9%), headache (10%), and dry mouth (9.1%).[39]

When examining the ability of reboxetine to prevent recurrence of depression, studies extending over several years with greater patient enrollment would be the ideal approach to assess efficacy. However, there have been relatively few long-term (several years) industry-sponsored maintenance studies of the newer antidepressants because such studies are expensive and not required for initial regulatory approval. However, several such studies have been completed or initiated and it is hoped that published data on maintenance therapy would soon become available for all the newer agents.[40,41]

Tolerability

As with efficacy data, it is important to examine tolerability both during acute treatment as well as over the long term. Some adverse effects (e.g., weight gain) may emerge only with continued therapy or following discontinuation (e.g., withdrawal symptoms). Sexual adverse effects may be underestimated in studies that rely only on spontaneous reporting. Some antidepressants are known for inducing troublesome adverse effects including sedation, tachycardia, blurred vision, constipation, weight gain, sweating, hypotension, difficulty urinating, and sexual dysfunction.[7] These effects can interfere with cognitive well-being as well as the ability to perform everyday tasks, thereby placing patients at risk for early discontinuation to avoid discomfort. The primary advantage of the newer antidepressants are their superior tolerability and higher compliance rates when compared with the older agents.

Versiani[42] pooled the tolerability information from the reboxetine clinical trials to assess the overall appearance of adverse effects. The patient population (n = 2613) was composed of both inpatients and outpatients who were diagnosed with major depression. Patients were treated with reboxetine, imipramine, fluoxetine, or placebo. The adverse events documented to occur more frequently with reboxetine therapy than with placebo included dry mouth (27% vs. 16%), constipation (14% vs. 8%), sweating (14% vs. 7%), insomnia (14% vs. 5%), urinary hesitancy (5% vs. 2%), tachycardia (5% vs. 2%), impotence (5% vs. 0%), and vertigo (2% vs. 0%). The numbers of patients opting to discontinue therapy were comparable for reboxetine (8%) and placebo (7.5%). With regard to comparative agents, the overall frequency of adverse effects was similar (reboxetine 73% vs. imipramine 76%, reboxetine 67% vs. fluoxetine 65%). Those events likely to develop with higher frequency with imipramine therapy included somnolence, tremor, hypotension, and dry mouth. When comparing reboxetine with fluoxetine, patients reported somnolence, diarrhea, and nausea significantly more frequently while taking fluoxetine; flushing, urinary hesitancy, paresthesias, hypotension, constipation, and dry mouth were documented significantly more in patients taking reboxetine. Data suggest that reboxetine-related adverse effects, such as constipation or dry mouth, appear to be mediated via the noradrenergic system.[7,10]

Kerr et al.[43] conducted a small study (n = 10, age 18–40 y) to examine the effects of reboxetine on psychomotor and cognitive function. Subjects were administered 0.5, 1, or 4 mg of reboxetine, 25 mg of amitriptyline, or placebo, in combination with alcohol or alcohol placebo; each patient served as his or her own control. A series of psychometric tests were administered to the participants to assess their functional performance at 1, 2.25, 3.5, 6, and 9 hours after dosing. The tests consisted of methods to assess Critical Flicker Fusion (CFF), Choice Reaction Time (CRT), and short-term memory. The CFF threshold was used to measure the overall processing capacity of the CNS and how psychoactive medications change this capacity. The CRT was a measure used to determine sensorimotor performance as well as the effect drugs can have on physical coordination. The scores following the testing procedures revealed that reboxetine had little or no effect on the measures compared with placebo, nor did it appear to interact with alcohol. Amitriptyline, on the other hand, significantly lowered CFF compared with placebo and/or reboxetine at all testing points, indicating an impairment in CNS function. In addition, amitriptyline slowed reaction time significantly ($p < 0.05$) compared with both placebo and reboxetine with alcohol. Amitriptyline also appeared to impair the short-term memory process. Therefore, reboxetine has minimal pharmacologic impact on psychomotor and cognitive function.

Drug–Drug Interactions

Since reboxetine is primarily metabolized by CYP3A4,[23] it is expected that inhibitors of this enzyme could result in increased plasma concentrations of reboxetine; therefore, administration of these agents with reboxetine should be done cautiously to avoid potential adverse effects.

A small (n = 13), single-dose, open-label study[44] was conducted to assess the drug interaction potential from the coadministration of ketoconazole 200 mg and reboxetine 4 mg. Ketoconazole is a potent inhibitor of CYP3A4. Patients were administered treatments in a crossover fashion: treatment A consisted of daily doses of ketoconazole 200 mg on days 1 through 5 and reboxetine 4 mg on day 2. After a one-week washout period, treatment B was initiated: rebox-

etine 4 mg administered on day 2. Ketoconazole administration resulted in significantly increased plasma concentrations of reboxetine, documented with AUC increases of 43–58%, decreases in oral clearances of 24–34%, decreases in elimination rates by 21–32%, and prolonged $t_{1/2}$ values of 4.5–6.7 hours for reboxetine enantiomers ($p < 0.05$). The time to reach maximum plasma concentrations was not significantly affected by ketoconazole administration. The most commonly reported adverse effects with coadministration were dizziness, pallor, nausea, vomiting, and constipation. Since there were documented alterations in reboxetine pharmacokinetic parameters, patients taking ketoconazole or other medications known to inhibit CYP3A4 (e.g., erythromycin, fluconazole, itraconazole) should be monitored for adverse effects or other manifestations that may indicate increased plasma concentrations of reboxetine.

Agents that induce CYP3A4 should also be used cautiously in combination with reboxetine due to the risk of suboptimal dosing levels. Phenytoin and rifampin are examples of medications that may decrease the plasma concentration of reboxetine secondary to their ability to induce CYP3A4.

Combination therapy with antidepressants having different mechanisms of action is used increasingly as an option for patients not responding to monotherapy. Therefore, drug interactions are an important consideration due to the potential for increased adverse effects or select manifestations such as serotonin syndrome. A small (n = 30), double-blind investigation[45] was conducted to assess the potential pharmacodynamic and pharmacokinetic interactions between reboxetine and fluoxetine. Subjects were randomized to eight days of therapy with reboxetine 4 mg twice daily/placebo once daily, fluoxetine 20 mg daily/placebo twice daily, or reboxetine 4 mg twice daily/fluoxetine 20 mg daily. The adverse effects most commonly noted by subjects included headache, dry mouth, paresthesias, dizziness, insomnia, and somnolence; those taking reboxetine alone did not report somnolence. The patient groups receiving reboxetine developed minor increases (<10 mm Hg) in supine systolic and diastolic blood pressure. Heart rate was significantly higher in subjects taking reboxetine; bradycardia was noted in those on fluoxetine. Fluoxetine did not appear to produce significant changes in reboxetine pharmacokinetic measures, including AUC, elimination rate, and oral clearance. The mean AUC for the *S,S* (+) enantiomer was 23% higher with coadministration of fluoxetine with reboxetine. Likewise, no significant changes in fluoxetine parameters were documented with coadministration of reboxetine. The AUC for fluoxetine was 25% higher following coadministration with reboxetine compared with fluoxetine alone. In addition, the pharmacokinetic parameters for the metabolite, norfluoxetine, were not significantly altered by coadministration of reboxetine.

Currently, there are no published data investigating the potential interaction between MAOIs and reboxetine. However, it is likely that concurrent administration of MAOIs with reboxetine will be contraindicated secondary to the serious reactions that have been documented with other antidepressants and MAOIs. Since monoamine oxidase metabolizes catecholamines (i.e., norepinephrine), inhibitors of this enzyme may allow norepinephrine to accumulate within adrenergic neurons. Therefore, concomitant reboxetine therapy could increase the risk of hypertensive crisis. Based on other recommendations for antidepressant therapy, a minimum washout period of 14 days is recommended prior to initiating reboxetine therapy in a patient taking MAOIs. When discontinuing reboxetine therapy, it is best to wait at least seven days prior to starting MAOI treatment.

It may also be prudent to avoid combining reboxetine with another potent noradrenergic reuptake inhibitor (e.g., desipramine) until data suggest otherwise. No recommendations can be made at present regarding combinations of reboxetine with other agents with noradrenergic activity (e.g., venlafaxine, bupropion, TCAs). Clinicians must use particular caution in the elderly or medically ill when considering such combinations. As with the use of any combination therapy, clinical judgment should guide therapy.

Reboxetine is extensively bound to plasma proteins.[21] Therefore, concurrent administration of drugs with a high affinity for plasma proteins, particularly α_1 acid glycoprotein, are at risk for shifting plasma concentrations of either drug. Potential agents that may compete with reboxetine for binding sites include propranolol and lidocaine.

Dosage and Administration

Reboxetine is expected to be marketed as 4-mg scored tablets. According to the currently published literature and product label in other countries where reboxetine is available, the recommended starting dose in adults is 4 mg twice daily. If an adequate response is not observed within three to four weeks of treatment, the dosage may be increased to a recommended maximum daily dose of 10 mg given in divided doses. For elderly patients as well as those with renal or hepatic impairment, it may be most appropriate to start therapy with 2 mg administered twice daily and increase as needed after several weeks of therapy. Due to lack of clinical experience, no recommendations can be made regarding dosing in children and adolescents.

Therapeutic Issues

Reboxetine is likely to be the first newer generation, selective NRI marketed in the US. Based on evidence supporting the role for norepinephrine in depression and its unique pharmacology, reboxetine can be expected to become a first-line agent for the treatment of major depression among both primary care and psychiatric practitioners. There appear to be subgroups of depressed patients who respond preferentially to noradrenergic agents. The patient types most likely to respond well to reboxetine include both outpatients and hospitalized patients with major depression (including first episode and recurrent depression) as well as depressed patients with prominent features such as low energy, decreased interests, weight gain, and concentration difficulties. Reboxetine is also likely to be a

promising investigational agent for treating adult attention deficit disorder as well as mood syndromes in dementia patients. Due to the receptor affinity preferences, reboxetine is less likely to cause cognitive, anticholinergic, cardiovascular, or sedative effects that are noted with TCA administration and gastrointestinal or sexual dysfunctions affiliated with SSRIs. At present, the most popular treatment options for SSRI failures (nonresponders or intolerance) include a trial with an alternative SSRI or augmentation with or switch to an agent in a different medication class. Data evaluating the role of reboxetine in SSRI failures are not currently available, but due to the differing mechanisms of action, reboxetine may prove to be a useful option in these clinical settings.

Reboxetine use has not yet been systematically studied in elderly patients with serious medical illness. Hence, it is prudent to use caution in such patients, especially those with preexisting risk factors for orthostatic hypotension, tachyarrhythmias, or urinary retention. Pending formal studies in children, no recommendations can be made for its use in this population. Given the importance of improving daily functional activities including work-related tasks in depressed patients, it may also be worthwhile for a future primary care study to compare the compliance rates and cost-effectiveness of reboxetine with the SSRIs. Comparator studies with other newer agents that are reported to have noradrenergic activity (e.g., bupropion sustained-release, venlafaxine extended-release) may also be worthwhile. Such data are likely to be critical for shaping both practice as well as managed care formulary decisions. As always, readers are encouraged to refer to the most current literature as well as the final package insert before prescribing since they may contain other relevant information as well as updated material that was not available at the time of this review.

Summary

The available data suggest that reboxetine will provide clinicians with another effective and safe option for treating depressive disorders in both inpatient and outpatient settings. Published clinical trials have shown reboxetine to be as effective as both SSRIs and TCAs, with positive results in both short- and long-term treatment periods. To date, reboxetine appears to be relatively well tolerated with a good safety profile. In addition, available pharmacokinetic data have documented few cytochrome P450–mediated drug interactions. Final FDA approval is not expected until completion and review of an additional US clinical trial. After final approval, reboxetine is expected to be a first-line agent for treating major depression as well as a promising alternative for patients who fail or cannot tolerate other antidepressant therapies.

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EXTRACTO

OBJETIVO: Repasar la farmacología, farmacocinética, eficacia, y tolerancia de reboxetina en el tratamiento de enfermedad depresiva mayor.

FUENTES DE INFORMACIÓN: Una búsqueda en MEDLINE, restringida a literatura en el idioma inglés, fue realizada por el período de 1966 a julio de 1999. Extractos y carteles presentados en reuniones también fueron revisados.

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: Los estudios disponibles al presente fueron conducidos en Europa. Los datos de estudios clínicos fueron revisados par coleccionar información específica sobre análisis de eficacia, parámetros farmacocinéticos, perfiles de tolerancia, e interacciones fármaco–fármaco. La información fue comparada con otros tratamientos antidepresivos cuando datos comparativos apropiados estuvieron disponibles.

SÍNTESIS: Reboxetina es un inhibidor selectivo de la recaptación de norepinefrina que ha demostrado ser un agente efectivo en el tratamiento de enfermedad depresiva mayor. En estudios clínicos, reboxetina fue efectivo en disminuir la media total de los resultados HAM-D en poblaciones de adultos. Las mejoras fueron similares entre reboxetina y desipramina, imipramina, y también fluoxetina. Reboxetina es tolerado relativamente bien, con insomnio, sudor, estreñimiento, y sequedad de la boco como eventos adversos reportados comúnmente. Hipotensión e irresolución urinaria ocurren en menor grado que con los tricíclicos, y comparado con fluoxetina, reboxetina está asociado con una proporción menor de naúsea, soñolencia, y diarrea. Ajustes en dosis podrían ser apropiados en pacientes ancianos y aquellos con deterioro renal y hepático.

CONCLUSIONES: Reboxetina ha recibido dos cartas de aprobación de la Administración de Drogas y Alimentos para el tratamiento de depresión mayor en adultos. Una vez se complete un estudio clínico adicional en los EU, es muy probable que reboxetina se convierta en un agente de primera selección en el manejo de enfermedad depresiva, y en una alternativa prometedora para aquellos que no han tolerado o que han fracasado los antidepresivos serotoninérgicos.

Brenda R Morand

RÉSUMÉ

OBJECTIF: Réviser les propriétés pharmacologiques et pharmacocinétiques ainsi que l'efficacité et la tolérabilité de la reboxétine lors d'usage pour le traitement de la dépression majeure.

REVUE DE LITTÉRATURE: Une revue de la littérature indexée dans MEDLINE, à partir de 1966 jusqu'en juillet 1999 a été effectuée. Les résumés d'exposés et d'affiches présentés lors de conférences scientifiques ont aussi été inclus dans la révision.

SÉLECTION DE L'INFORMATION ET DES ÉTUDES: Les publications disponibles au moment de la révision résultaient d'études européennes. Les résultats des essais cliniques furent révisés afin de rassembler l'information spécifique aux analyses d'efficacité, aux paramètres pharmacocinétiques, aux profils d'effets indésirables, et aux interactions médicamenteuses. Cette information fut comparée à celle des autres thérapies anti-dépressives, lorsque des données adéquates étaient disponibles.

RÉSUMÉ: La reboxétine est un inhibiteur sélectif de la recapture de la norépinéphrine ayant démontré une efficacité dans le traitement de la dépression majeure. Lors des essais cliniques, la reboxétine a significativement diminué le score total moyen obtenu avec l'échelle de Hamilton (HAM-D) auprès d'une population adulte. L'amélioration observée des symptômes dépressifs s'est révélée comparable avec la reboxétine, la désipramine, l'imipramine, et la fluoxétine. La reboxétine est relativement bien tolérée quoique des effets indésirables mineurs tels que l'insomnie, la sudation, la constipation, et la xérostomie soient fréquemment rapportés. L'hypotension et la rétention urinaire sont plus rarement observées avec la reboxétine qu'avec les agents tricycliques. De plus, la reboxétine est associée à moins de nausée, de somnolence, et de diarrhée que la fluoxétine. Des ajustements posologiques peuvent être requis chez les personnes âgées et les personnes présentant une atteinte rénale ou hépatique.

CONCLUSIONS: La reboxétine a reçue deux lettres favorables de l'Administration des Drogues et Alimentaires pour le traitement de la dépression majeure de l'adulte. Il est fort probable, qu'après l'achèvement d'un essai clinique supplémentaire réalisé aux EU, la reboxétine devienne un agent de première ligne pour le traitement de la dépression majeure. Celle-ci offrira une alternative prometteuse pour les personnes n'ayant pas répondu ou n'ayant pas toléré des antidépresseurs sérotoninergiques.

Marie-Claude Vanier